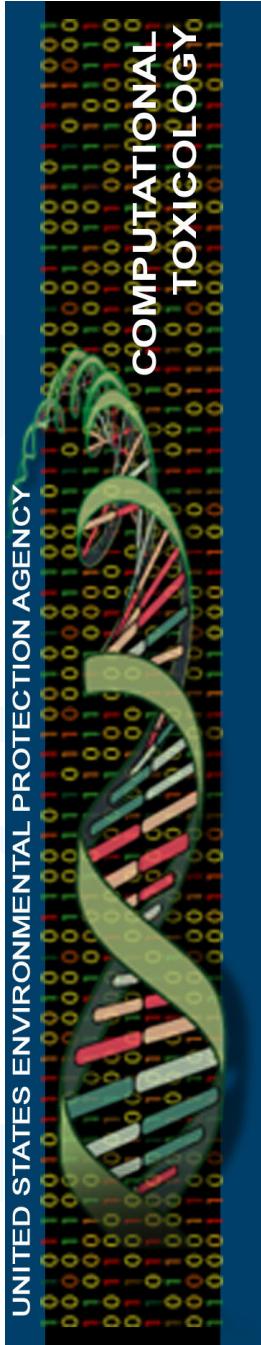


Improving Exposure Science for Screening, Prioritizing and Toxicity Testing

JRC/ECETOC Workshop on Exposure and Risk Assessment
of Chemical Mixtures in Consumer Products
JRC, Ispra, Italy. 29/30th January 2009

Elaine Cohen Hubal
National Center for Computational Toxicology

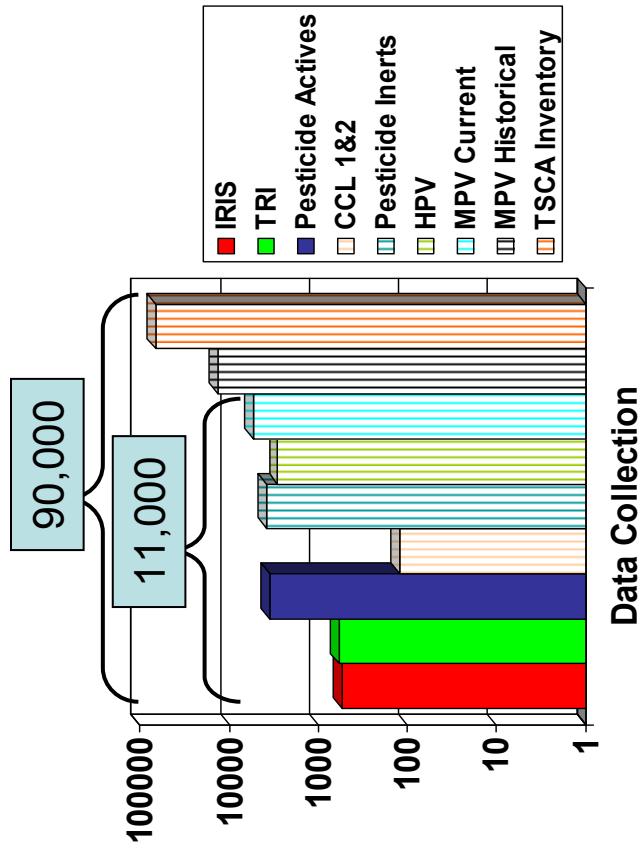


Goal Statement

Advance the characterization of exposure science required to *translate* advances and findings in computational toxicology to information that can be directly used to support exposure and risk assessment for decision making and improved public health.

Mandate to Assess Thousands of Chemicals

Clear need to develop methods to evaluate a large number of environmental chemicals for their potential toxicity



- CEPA Prioritization Program (DSL)
- REACH
- HPV
- Endocrine Disruptor Screening Program (EDSP)
- Chemical Assessment and Management Program (ChAMP)

Toxicity Testing in the Twenty-first Century

- The key aspect of the NRC vision and the proposed paradigm shift in Toxicity Testing is that new tools are available to examine toxicity pathways in a depth and breadth that has not been possible before.
- Efforts underway to apply high-throughput-screening (HTS) approaches for chemical prioritization and toxicity testing have been accelerated in response to NRC reports.
- An explosion of HTS data for *in vitro* toxicity assays will become available over the next few years.

Toxicity Testing in the Twenty-first Century: A Vision and a Strategy

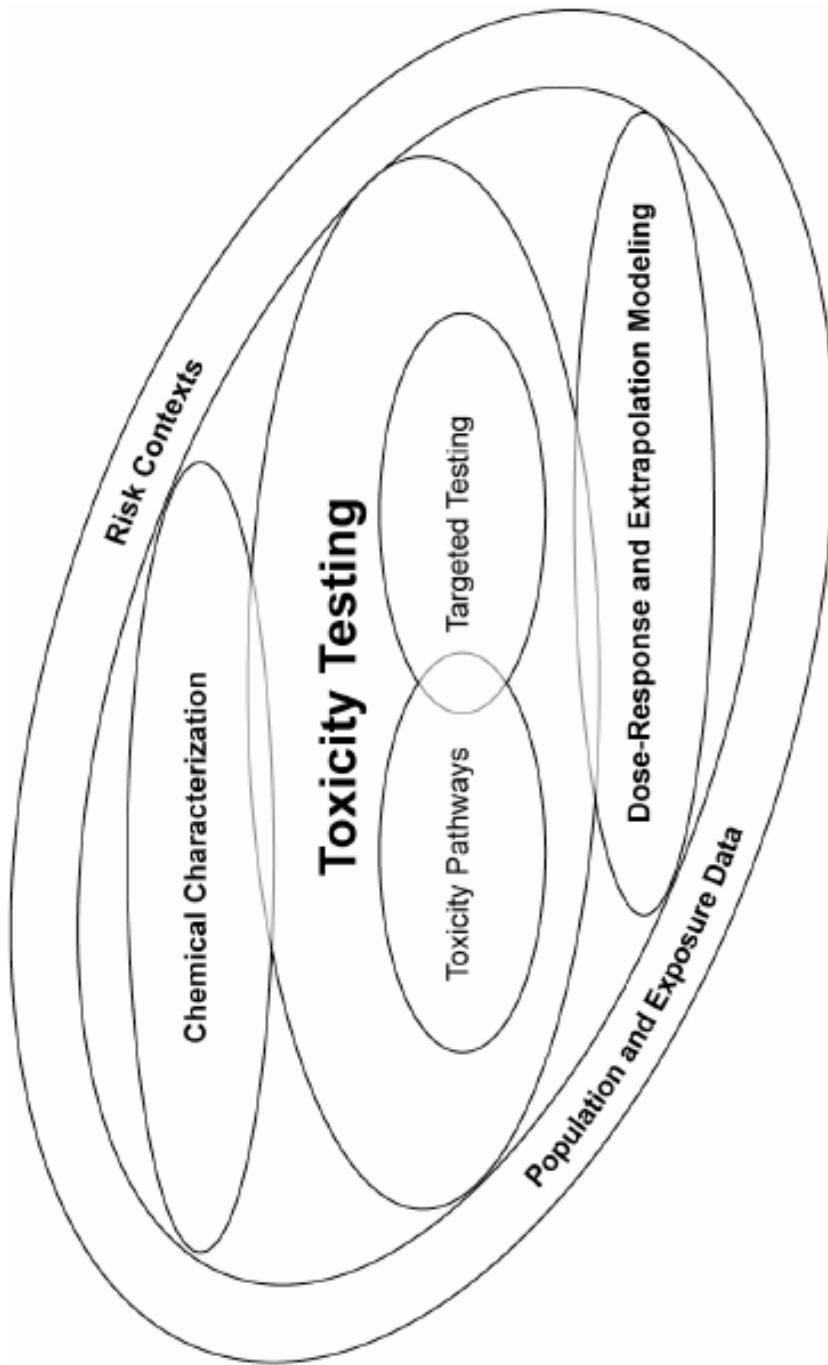


FIGURE 2-3 The committee's vision is a process that includes chemical characterization, toxicity testing, and dose-response and extrapolation modeling. At each step, population-based data and human exposure information are considered, as is the question of what data are needed for decision-making.

Exposure Science in NRC Vision

- Population-based data and human exposure information required at each step of vision; critical role in both guiding development and use of the toxicity information. Components include:
 - Use of information on host susceptibility and background exposures to interpret and extrapolate *in vitro* test results.
 - Use of human exposure data to select doses for toxicity testing so we develop hazard information on **environmentally-relevant effects**.
 - Use of biomonitoring data to relate real-world human exposures with concentrations that perturb toxicity pathways to identify potentially important (**biologically-relevant**) exposures.

ToxCast™ Program for Prioritizing Toxicity Testing of Environmental Chemicals

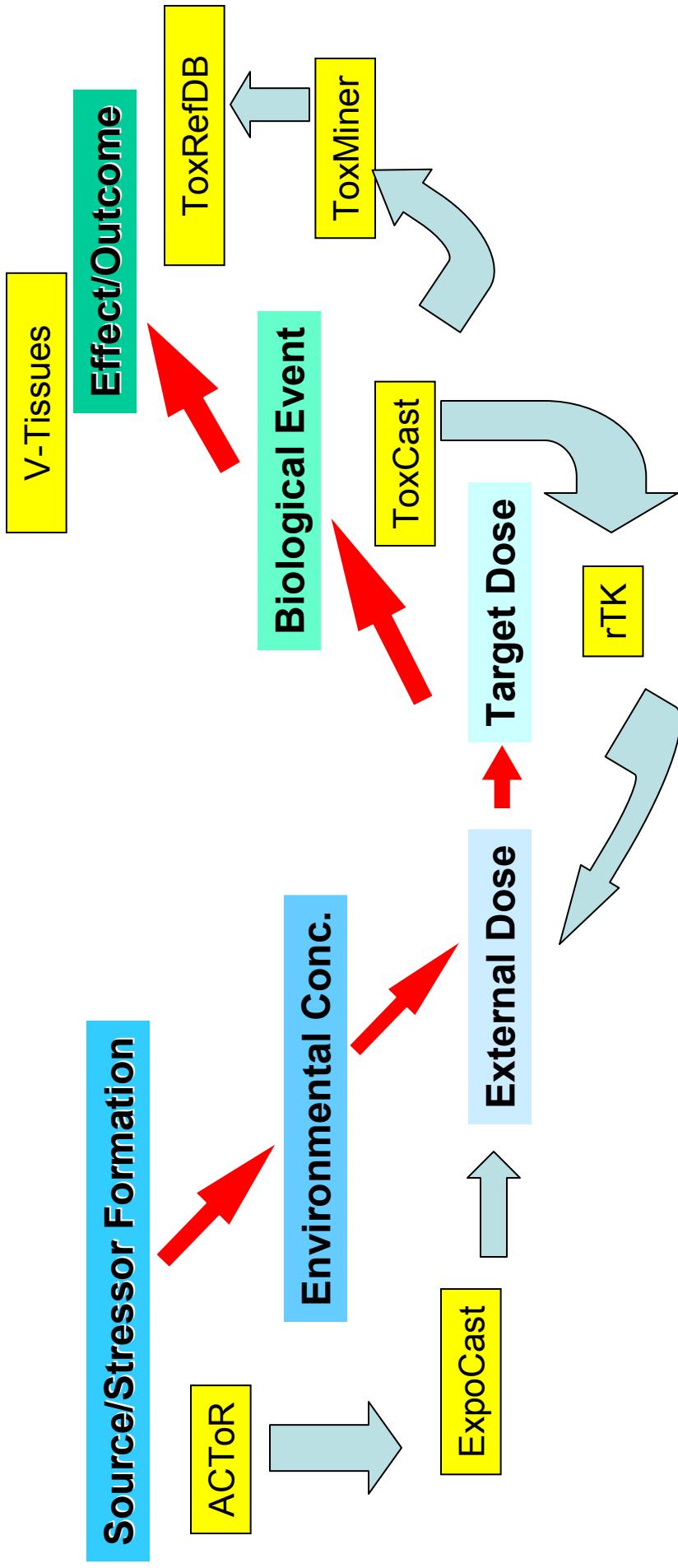
- In 2007, EPA launched ToxCast™ in order to develop a cost-effective approach for prioritizing the toxicity testing of large numbers of chemicals in a short period of time.
- Using data from state-of-the-art high throughput screening (HTS) bioassays developed in the pharmaceutical industry, ToxCast™ is building computational models to forecast the potential human toxicity of chemicals.

<http://epa.gov/ncct/toxcast/>



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Source to Outcome Continuum



Exposure Science for Toxicity Testing

- How can we characterize exposure efficiently and support development of toxicity information to facilitate prioritization of thousands of compounds?
- Paradigm shift in exposure science required
 - From resource and time intensive measurement and modeling
 - To rapid, inexpensive approaches for characterizing and predicting **biologically-relevant** exposure.
 - Leverage advanced and emerging technologies and approaches

Priority Exposure Research for Computational Toxicology

With NCCT and NERL have identified the following priority research areas (Sheldon and Cohen Hubal, submitted):

- Accessible and linkable exposure databases.
- Exposure screening tools for accelerated chemical prioritization
- Computational tools for exposure-dose reconstruction and source-to-outcome analyses
- Efficient monitoring methods for assessing risk (biologically-relevant exposure metrics)

Human vulnerability and life-stage aspects are integral to each of these.

Accessible and Linkable Exposure Databases

- Easily accessible, chemically indexed exposure databases that can be linked with toxicity databases are required to facilitate application of environmental informatics tools for risk assessment.
- Developing exposure data bases and linking them with ACToR to better understand current state of knowledge
- Link through ACToR with DSSTox so that chemical structure can also be related to exposure and hazard
 - Links to publicly available use data and systematic (machine learning?) approach for interrogating data through these links (or simply out on internet?)
 - Human exposure knowledge base

Exposure Screening Tools for Accelerated Chemical Prioritization

- Critical review of existing approaches
- Scenarios
 - standardized, publicly available libraries
 - systematic approaches for selecting/prioritizing scenarios
 - E.g., Machine learning and data analysis of marketing data to help NERL simulate human activity patterns and behavior
- Sentinel products – systematic approach for selection
- Screening models/modules – basis for selection
- Screening-level indices for efficient screening and prioritization of chemicals based on potential for exposure (define exposure landscape)
- Mining and evaluation of extant exposure data to better characterize important determinants of exposure and to identify gaps in data required to screen and prioritize potential for exposure
 - Exposure knowledge base

Computational Tools for Exposure-Dose Reconstruction and Source-to-outcome Analyses

- Novel computational approaches to ensure hazard information is developed on environmentally-relevant effects.
- Computational tools and approaches for characterizing biologically-relevant exposure to select doses for toxicity tests and to interpret and extrapolate results of *in vitro* tests
- Application of advance computational approaches for dose reconstruction to relate biomarkers of exposure in populations with administered concentrations of *in vitro* HTS assays.
- Coordinated development to provide exposure, dose-response, and biological pathway models that use common programming languages to facilitate links across the source-to-outcome continuum.

Efficient Monitoring Methods for Assessing Risk (Biologically-Relevant Exposure Metrics)

- Improved mechanistic understanding of exposure processes and determinants
- Translation of advanced toxicogenomic (e.g. metabonomic) and biosensor technologies to measure biologically relevant exposures and identify susceptible individuals.

A Path Forward: Anchoring Stressors to Real-World Human Exposure

- The NRC Vision of a shift to characterizing toxicity pathways requires a commensurate shift to characterizing exposure across all levels of biological organization.
- Interpretation of toxicogenomic hazard data requires contextual relevance. Pathways identified using HTS approaches are being anchored to apical endpoints using conventional toxicity data.
- Similarly, understanding relevant perturbations leading to these toxicogenomic endpoints requires anchoring stressors to real-world human exposure.
- New approaches to risk assessment require exposure science to predict exposures down to the molecular level. Requires systems-based consideration of interactions between exposure and effect.



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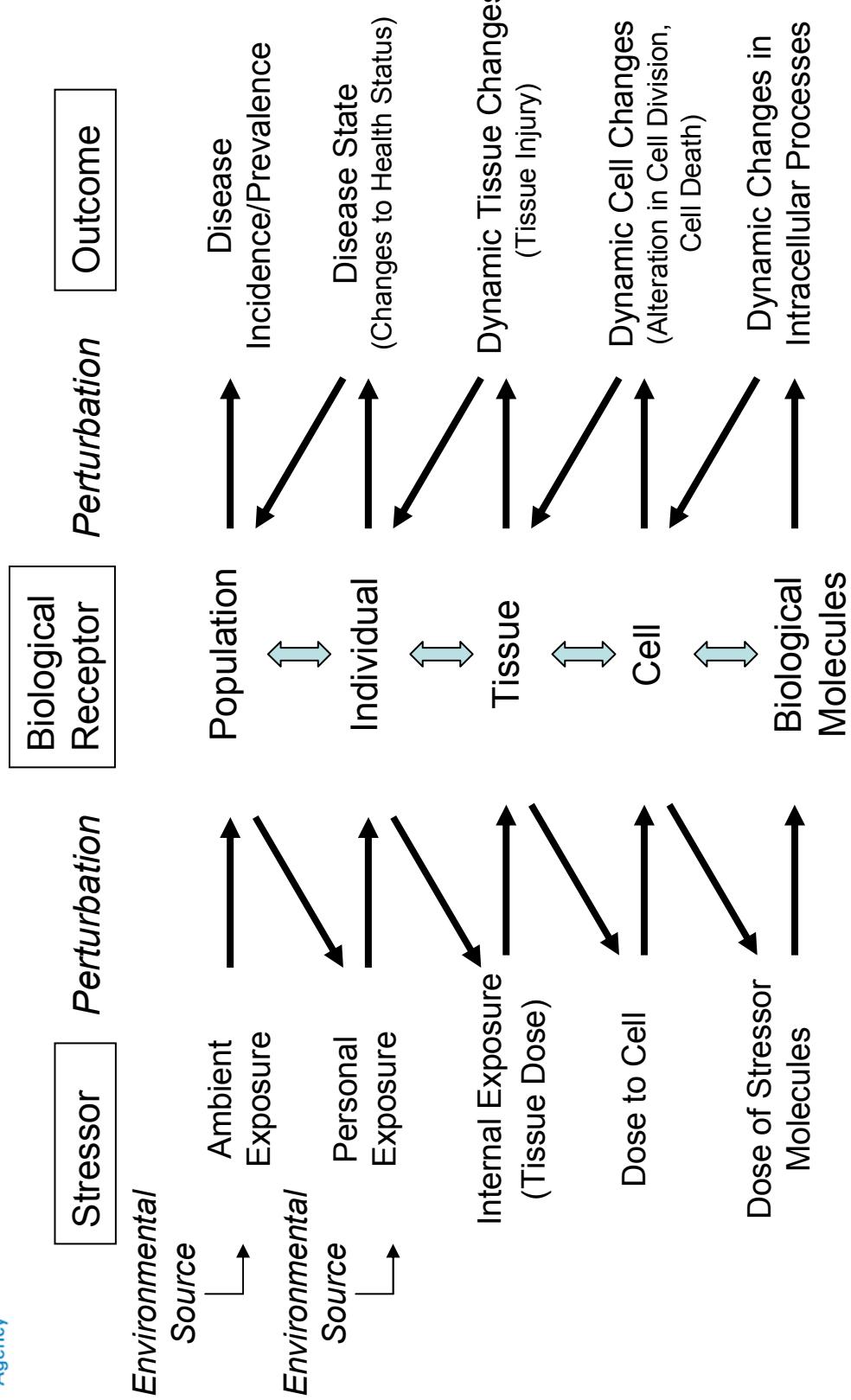


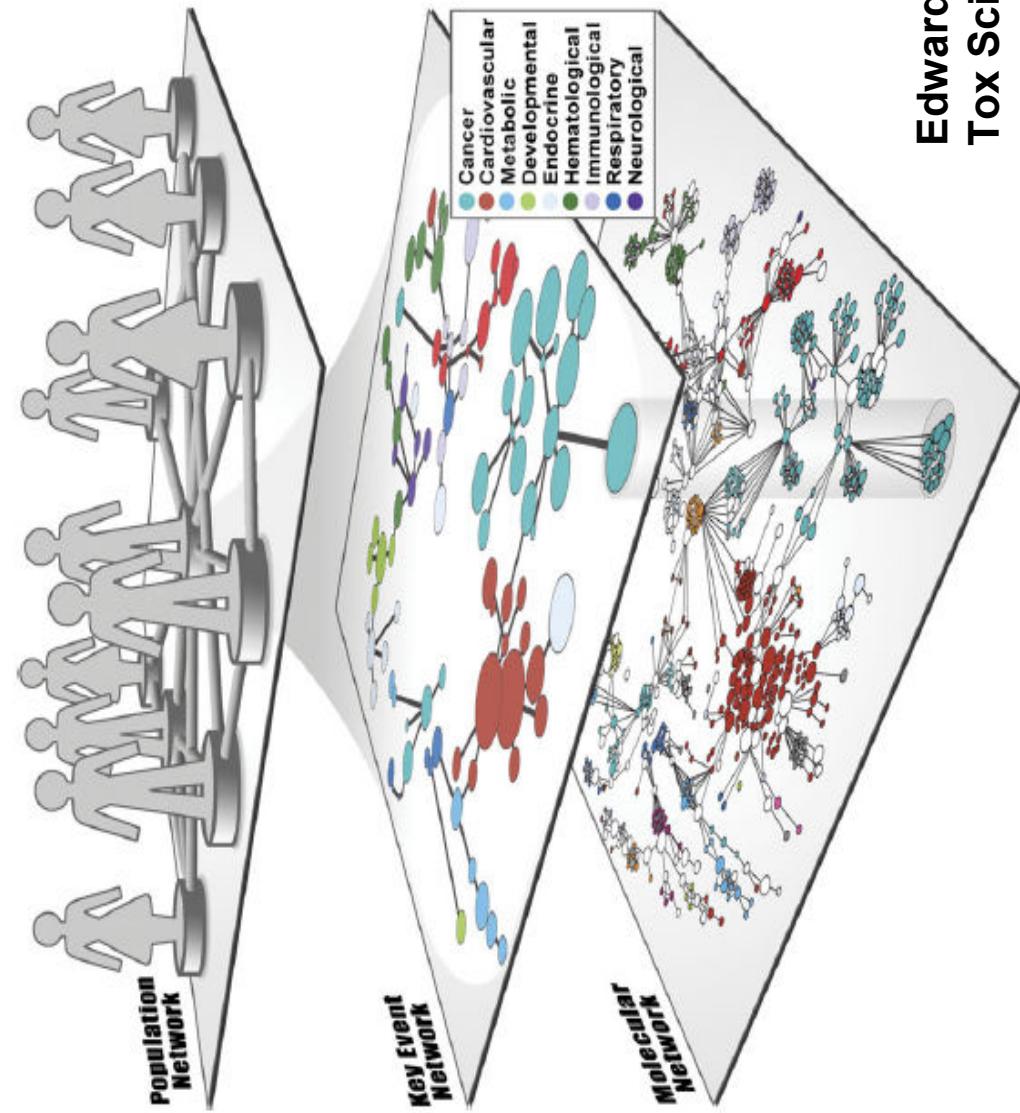
Figure 11
National Center for Computational Toxicology

JESSE, 2008



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Incorporating Network Analysis into Risk Assessment



Edwards and Preston,
Tox Sci, 2008

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EPA Community of Practice: **Exposure Science for Toxicity Testing, Screening, and Prioritization**

- The primary purpose of the EPA Exposure Science Community of Practice (ExpoCoP) is to provide a forum for promoting the advancement and utilization of exposure science to address Agency needs for chemical screening, prioritization and toxicity testing.
- Membership of well over 40 individuals from over 15 public and private sector organizations
- http://epa.gov/ncct/practice_community/exposure_science.html

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- NERL – Linda Sheldon

Disclaimer

Although this work was reviewed by EPA and approved for presentation, it may not necessarily reflect official Agency policy.